

Taking the fun out of psilocybin: Can psilocybin's rapid antidepressant action be preserved in the absence of hallucinations?

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Abstract

Major depression is a debilitating illness and one of the leading causes of disability worldwide. First line pharmacotherapies targeting the serotonin system, such as selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, are effective in ~60% of patients. Typically, patients must take SSRIs for 4-8 weeks to experience relief of depressive symptoms. More effective and faster acting medications are needed. Recently, psilocybin, a hallucinogenic plant-derived pan-serotonergic agonist, was shown to produce a rapid antidepressant response in humans with treatment resistant depression. However, the hallucinations pose a significant barrier to its widespread use. Antagonists of serotonin2A receptor (5-HT2AR), such as ketanserin, can be used to block hallucinations in humans. Can a combination of psilocybin plus ketanserin provide rapid relief of depressive symptoms without hallucinations? In rodents, chronic administration of fluoxetine reverses anhedonic deficits in reward behavior produced by chronic multimodal stress (CMS). Fluoxetine also restores the strength of temporoammonic (TA) - CA1 synapses in the hippocampus. Here, we test the hypothesis that psilocybin can exert a rapid anti-anhedonic effect in rodents subjected to CMS and ask whether this effect is independent of 5-HT2ARs. Using 10-21 days of CMS, we induced an anhedonic phenotype in rodents, as assessed by loss of sucrose preference. Sucrose preference was restored within 48 hours of a single acute dose of psilocybin (1mg/kg). Experiments with psilocybin and ketanserin are in progress. Ketanserin did not impair the ability of fluoxetine to restore sucrose preference and to strengthen TA-CA1 synapses, suggesting that psilocybin's antidepressant effect may also be independent of 5-HT2ARs. Blocking the hallucinogenic side effect of psilocybin, but not the rapid acting antidepressant effect, by co-administering psilocybin and ketanserin could provide a novel and viable approach for safe and effective rapid relief of depression.